REMARKS

Claims 1-5, 7-13, 16-19, 21, 24-29, 31, and 58-59 are pending in the application. Claims 6, 14-15, 20, 22-23, 30, and 32-57 were previously cancelled. Claims 1, 7, 10, 26-27, and 58 are amended. Support for the amendment can be found, for example, on page 10, line 9 of the application as filed. No new matter is added by the amendment.

Withdrawal of rejection of claims under 35 U.S.C. §102

Applicant thanks the Examiner for withdrawal of the rejections in view of Watson.

Claim Objections

The Examiner has objected to claims 1-5, 7–13, 16–19, 21, 24-29, 31, and 58-59 for minor informalities. The Examiner argues that the claims recite measuring biomarker, Marker I (BC1), Marker II (BC2), Marker III (BC3)…which are neither recognized names or structures in the art nor defined in the specification." Applicants disagree.

Without agreeing with the Examiner, Applicant has cancelled the language BC1, BC2, and BC3 from the claims. No change of scope is made by the amendment as BC1 is the same as Marker I, BC2 is the same as Marker II, and BC3 is the same as Marker III. Applicant submits that the specification provides detailed structural information about each of the markers, e.g., their molecular weight as determined by SELDI, methods of which are well known in the art and provided in the specification, which provides molecular weights within about plus or minus 0.15% of the molecular weight claimed, and their presence in serum from a human subject. Applicant submits that one of skill in the art, *i.e.*, one capable of performing SELDI, would be able to determine if peaks in a spectra included the markers claimed.

The SELDI method of molecular diagnostics relies on pattern recognition based on molecular weight of low molecular weight protein fragments in a serum sample and does not require identification of the specific peptides by sequence. As discussed by Petricon and Liotta (*Curr. Opin. Biotech.* 15:24-30, 2004, copy enclosed),

> MS analysis of the low molecular weight range of the serum/plasma proteome is a rapidly emerging frontier for biomarker discovery and clinical diagnostics…. Using this approach, **the pattern itself, independent of the identity of the proteins or peptides, is the discriminator and my be clinically**

> **useful immediately before the underlying identities are eventually discerned**. (page 28, column 2, third full paragraph, emphasis added)

Therefore, one of the advantages of the SELDI based method of diagnosis is that it allows for detection and identification of proteins for diagnostic purposes **without** needing to know the specific protein sequence or identity. One of skill in the art would understand the definitions, further supported by the molecular weights as now claimed, to provide sufficient structural information about each marker.

Applicants respectfully request that the objection be withdrawn.

Rejection of Claims 1-13, 16-19, 21, 23-31 and 34 Under 35 USC 112, First Paragraph

The Examiner has indicated that claims 1-5, 7-13, 16-19, 21, 23-25 and 58 remain rejected under 35 USC 112, first paragraph for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Office Action asserts that:

> 1) The biomarkers having MW about 4283, (BC-1), about 8126 (BC-2) and about 8932 (BC-3) are not used as recognized marker for any cancer including breast cancer…. One could find many proteins presented in the serum samples of breast cancer patients which could be broken to fragments having such molecule weight when they are applied to mass spectroscopy.

Applicant respectfully disagrees. Until the instant invention, the claimed markers were not recognized. The instant invention includes the identification of the markers by SELDI. The assertion that proteins fragments of any size could be found in a serum sample is contradicted by the teachings of the instant application in which the same markers were identified repeatedly in multiple subjects, and the presence of the markers was later confirmed in a completely separate cohort of subjects. This demonstrates that the markers can be repeatedly and conclusively identified using the claimed method, SELDI that have a molecular weights within the tolerable range of +/- 0.15% of the claimed value. Applicant respectfully requests that the Examiner support the assertion that fragments of essentially any size could be routinely found in serum from subjects, properly handled using routine clinical methods to preserve samples. The entire field of SELDI-based diagnostics relies on the ability to identify proteins by their molecular weights repeatedly in serum samples from subjects having a particular disease. The assertion of the Examiner suggests that the entire field of SELDI-based diagnostics is inoperable.

Petricon and Liotta discuss the diagnostic value of analysis of the peptide fragments analyzed by SELDI.

> Thus, even if these small enzymatically generated peptide fragments are far removed from the actual disease, they are not merely 'epiphenomena' and can retain specificity for the disease **because the process that generated the clipping in the first place can arise within the uniqueness of the disease tissue microenvironment**. (page 24, column 2, first paragraph, emphasis added)

Further, the SELDI method of molecular diagnostics relies on pattern recognition based on molecular weight of low molecular weight protein fragments in a serum sample, as discussed above, and does not require identification of the specific peptides by sequence. Applicant notes that even Diamandis, who questions the value of the diagnostic markers, does not question the ability to definitively identify the protein peaks indicated based on their molecular weight as determined by SELDI. Applicant submits that one of skill in the art of SELDI based diagnostics would be able to use the claimed markers for the claimed diagnostic methods.

The Office Action (in point 2) further questions the significance of the results in view of the relatively large standard deviations. The observed standard deviation include analytical variability which can be reduced in assay development if the biomarker is to be used in clinical applications. Such methods are provided in the specification, see, e.g., Data Analysis section starting on page 45. The data presented are those from the process of identification of the markers, which are demonstrated in the instant application to be useful in breast cancer diagnosis and monitoring.

Furthermore, how much "separation" in the distributions of a biomarker among different patient groups will depend on the specific clinical application, and cut-offs can be selected based on clinical considerations well known in the art to provide a test with the desired sensitivity and specificity. The instant invention provides a minimally invasive method to test for breast cancer. It is well known that mammography has a relatively high false negative rate, and breast MRI can have a relatively high false positive rate, leading to unnecessary biopsies. Providing a minimally invasive preliminary screening assay to select those who should be further examined is useful, even if the assay alone may not be conclusive.

A biomarker with significant overlap could still be clinically useful. For example, if a biomarker overlaps among 80% of the disease and non-disease group for a slow-progressing

disease (e.g., a large proportion of prostate cancer) and the workup procedure (e.g. biopsy) itself could lead to over treatment and additional complications, one can choose a cutoff such that only the 20% of true negatives (and therefore capture almost all the positives) are called negative, resulting a test with very high sensitivity and low specificity. This test however will have a very high negative predictive value and can be used to reduce unnecessary workup procedures. For higher sensitivity and specificity, more markers can be analyzed, with cut-offs appropriately adjusted. Clinical tests are not and need not be perfectly sensitive or specific to be useful.

It is noted that some widely used and well known markers, such as PSA show statistical overlap in positive and negative pools. PSA by itself does not have the statistical power to discriminate cancer from non-cancer, as levels of PSA also significantly overlap, sometimes PSA can be even higher, in the non-cancer patient populations. However, in lieu of other available clinical information, PSA level becomes very informative. For early detection, serial PSA measurements on the same patient (PSA velocity) is used to predict the likely hood of cancer, so patients can be spared of unnecessary biopsies. For disease management, PSA level, help the doctor to predict the chance of organ confined prostate cancer.

Applicant also points to the specification that demonstrates the utility of the markers for the identification of subjects having breast cancer (see page 30, lines 8-14):

> For example, use of only three of these biomarkers, 4283 (BC1), 8126 (BC2) and 8932 (BC3), **93% of breast cancer patients were correctly identified at the following stages**: Stage 0/I (93%), stage II (85%) and stage m (94%). With only one biomarker (BC3), 85% of breast cancer patients with stage 0/I (88%), stage II (78%) and stage III (92%), were correctly identified. Thus, a mere detection of one or more of these markers in a subject being tested indicates that the subject has progressed to a different clinical stage of the tumor. (emphasis added)

Applicant notes that a similar statement was made by the inventors in the paper that appeared in the peer-reviewed journal *Clinical Chemistry* (Li et al, 2002, 48:1296-1304, copy enclosed, see second paragraph of Discussion, page 1302) that served as the basis for the patent application. The reviewers of the manuscript, *i.e.*, those of skill in the art, found the data and analysis valid and sufficiently important to recommend the publication of the manuscript in the journal.

> Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d

1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Applicant submits that no reason has been provided to doubt the truth of the statements made in the application regarding the usefulness of the markers for the detection of breast cancer. Those of skill in the art, allowing publication of a manuscript including the same data, did not doubt the truth of the statements regarding the usefulness of the markers for detection. In the absence of a demonstration that the analysis provided in the specification is incorrect, the demonstration that the markers can be used to detect breast cancer with high sensitivity and specificity must be accepted by the Examiner.

The Examiner points to the later publication of the inventors to suggest that the markers identified in the instant application are not useful for the diagnosis of breast cancer. Applicant respectfully disagrees.

The variation in marker detection could be explained by a number of reason, including difference in study populations. Breast cancer is a very heterogeneous disease. Variations in patient composition (stage, histological/molecular subtypes, etc) can result in changes in expressions of potentially disease related biomarkers. Applicant notes that this statement was considered by those of skill in the art, i.e., the reviewers of the manuscript, to be a valid statement. Further, Applicant notes that a change in Marker I/BC1 was still observed in the later paper of the inventors.

Not all markers, even those confirmed to be associated with cancer, are effective in all cases and all subjects. For example, evaluation of the effectiveness of p53 as a prognostic factor have resulted in both positive and negative conclusions in studies. More recent studies suggest that its expression patterns may depend on specific molecular subtypes of the disease (e.g., triple negative breast cancer, ref: Byung Joo Chae et al., p53 as a Specific Prognostic Factor in Triple-negative Breast Cancer, *Japanese Journal of Clinical Oncology* Advance Access published on March 20, 2009, DOI 10.1093/jjco/hyp007.)

The Li et al. 2005 reference cited by the Examiner indicates that Marker I (referred to as BC1 in the reference) may be limited in its use as a stand alone marker, but may be useful in a multimarker panel (see abstract). This is sufficient to make the use of the marker enabled.

Applicant points to the Training materials for examining patent applications with respect to 35 U.S.C. section 112, first paragraph- enablement of chemical/ biotechnical applications (http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#iiib1) regarding how claims to diagnostic assays should be construed. A portion of the text is reproduced below for convenience.

> (III)(A)(2)(b)(ii)((b)) Diagnosis Assays
>
> Unless a specification specifically states something to the contrary, the term **"diagnostic assay" is to be construed to mean any assay that can be used to help diagnose a condition,** as opposed to an assay that can, in and of itself, diagnose a condition. A diagnosis is typically made by evaluating the results of several screening assays, each of which has some level of false results and, accordingly, each of the screening assays would be a "diagnostic assay". Therefore, to enable a diagnostic assay use, a disclosure merely needs to teach how to make and use the assay for screening purposes.

Therefore, the potential usefulness of Marker I/ BC 1 in a diagnostic assay, which is expected to be considered in conjunction with one or more other diagnostic assays, is sufficient to meet the enablement requirement as set forth in the guidelines from the Office.

The comments in the letter of Diamandis are considered, however, it is noted that the letter is not peer reviewed, and that Diamandis is presently an editor of the journal *Clinical Chemistry*, and it believed to have been an editor at the time of the publication of the letter. Further, the letter of Diamante does not state that the data or the analysis are incorrect, but that "In **my opinion**, the data… are rather disappointing" (emphasis added). The value of the opinion of one person must be considered against the data, the statements of the inventors, and the published peer reviewed manuscript.

Withdrawal of the rejection is respectfully requested.

Rejection of Claims Under 35 USC 102(e)

The Examiner has rejected claims 1, 2, 4-8, 10, 11, 17-19, 21, 23, 24, 26-28, 30 and 58 as being anticipated by Mutter et al. As indicated above, the claims have been amended to indicate the molecular weights of the claimed biomarkers, and the amount of variation in molecular weight detection using SELDI methods. Mutter et al. does not teach or suggest the biomarkers as currently claimed.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejections Under 35 USC 103(a)

The Examiner has rejected claims 1-3, 8-12, 26 and 29 under 35 USC 103(a) as being unpatentable over Mutter in view of Lauro et al. and/or Gion et al. As indicated above, the amended claims are not anticipated and are not made obvious by Mutter. Neither Lauro nor Gion make up for the deficiencies of Mutter.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

FEES AND REQUEST FOR EXTENSION OF TIME FOR REPLY

Applicant hereby requests a three month extension of time for reply. The Commissioner is authorized to charge fees for a three month extension in time for response and a Request for Continued Examination, small entity, to Deposit Account 04-1105 referencing Docket No. 57203(71699). It is believed that there is no further fee due with this response. However, if an additional fee is due with this paper or any other paper filed by this Firm in relation to this application, the Commissioner is authorized to charge the Deposit Account above. Refund of overpayment is respectfully requested. In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: September 14, 2009

Respectfully submitted,

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